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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,028	03/24/2005	Sarina Striem	800.1019	9002

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EXAMINER	
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ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,028	STRIEM ET AL.	
	Examiner	Art Unit	
	Taylor Victor Oh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/04/10*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-35,38-40 and 45-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-35,38-40,45 and 46* is/are rejected.

7)☒ Claim(s) *32 and 47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/04/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/04/10 has been entered.

Non-Final Rejection

The Status of Claims

Claims 32-35, 38-40, and 45-47 are pending.

Claims 32-35, 38-40, and 45-46 are rejected.

Claim 47 is objected.

Claim Objections

Claim 32 is objected to because of the following informalities:

In claim 32, the phrase" cancer metastatis" is recited. This expression is mis-spelled.

Appropriate correction is required.

Claim 47 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-35, 38-40, and 45-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the glioma treatment, does not reasonably provide enablement for the treatment or management of a metalloproteinase-related disease or disorder selected from cancer metastasis recited in claim 32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The scope of the claims is not adequately enabled solely based on the metalloproteinase inhibitor activity for treating cancer metastasis provided in the specification. The claims are directed to the treatment of generic cancer metastasis by using only the mechanistic nature of inhibiting matrix metalloproteinase enzymes. However, this kind of a generic treatment for cancer metastasis has confronted with a serious shortcoming in view of the teachings of Isaiah J. Fidler (Cancer Research, 50,

1990, p.6130-6138), who has pointed out the major issue for treating cancer metastasis in the followings:

> The major barrier to the treatment of metastases is the biological heterogeneity of cancer cells in primary and secondary neoplasms. This heterogeneity is exhibited in a wide range of genetic, biochemical, immunological, and biological characteristics, such as cell surface receptors, enzymes, karyotypes, cell morphologies, growth properties, sensitivities to various therapeutic agents, and ability to invade and produce metastasis (1–5, 10–15). Moreover, it is important to remember the term "cancer" denotes a collection of malignancies, with each cancer of each organ consisting of numerous subsets. This tremendous heterogeneity is probably due to the different etiologies, origins, and selection pressures of different cancers.
>
> Continual empiricism in the treatment of cancer is unlikely to produce significant improvement. Therefore understanding the mechanisms responsible for the development of biological heterogeneity in primary cancers and in metastases and the process by which tumor cells invade local tissues and spread to distant organs is a primary goal of cancer research. Only from a better understanding will come the ability to design more effective therapy for different cancers and improvements in the way physicians deal with cancer metastasis. My lecture, therefore, reviews recent data that provide some answers to these difficult questions.

Furthermore, Fidler expressly specifies that the outcome of metastasis is influenced by the intrinsic properties of tumor cell and host factors as described below in table 1:

Table 1 ***Properties of tumor cells and host factors that regulate cancer metastasis***

I. Tumor cell properties
  A. Facilitation of metastasis
    1. Production of growth factors and their receptors.
    2. Production of angiogenic factors.
    3. Motility, invasiveness.
    4. Aggregation, deformibility.
    5. Specific cell surface receptors and adhesion molecules.
  B. Inhibition of metastasis
    Antigenicity.

II. Host factors
  A. Facilitation of metastasis
    1. Neovascularization.
    2. Paracrine and endocrine growth factors.
    3. Platelets and their products.
    4. Immune cells and their products.
  B. Inhibition of metastasis
    1. Tissue barriers.
    2. Blood turbulence, endothelial cells.
    3. Tissue inhibitors of degradative enzymes.
    4. Tissue antiproliferative factors.
    5. Immune cells and their products.

Therefore, the specification falls short because data essential for treating generally the heterogeneity of cancer metastasis by means of only inhibiting matrix metalloproteinase enzymes is not fully described in the specification.

In evaluating the enablement in question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors

include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The Nature of the Invention

The nature of the invention in claim 32 is as followed:

32. (currently amended) A method for treating or managing a ~~disease associated with an elevated~~ metalloproteinase (MMP) or calpain related disease or disorder in a mammal ~~as compared to the control level of metalloproteinase (MMP) or calpain found in a normal mammal~~ , the disease or disorder being selected from the group consisting of cancer metastatis and glioma comprising administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the Formula (I):

a

The State of the Prior Art

The state of the prior art is that according to US Patent No. 5,948,780, MMP inhibitors have been used to prevent and treat congestive heart failure and other cardiovascular diseases. Recent data has revealed that specific enzymes are closely related to some diseases ,while there is no effect on other diseases. The MMPs are generally classified based on their substrate specificity; particularly , the collagenase subfamily of MMP-1, MMP-8, and MMP-13 selectively cleave interstitial collagen tissue. This has been noticed by the discovery that only MMP-13 is over expressed in breast carcinoma, whereas MMP-1 alone is over expressed in papillary carcinoma (see Chen

et al., J. Am .Chem. Soc., 2000;122;9648-9654). Furthermore, according to Wo/01/63244A1 and US Patent No. 6,008,243 few selective inhibitors of MMP-13 have been approved.

> Stable lipophilic diesters of the divalent metal ion chelator 1,2-bis(2 aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA) have been disclosed in the International Patent Publication No. WO 99/16741 of the same applicant. Also disclosed in this publication is the use of these compounds in pharmaceutical compositions useful for treating diseases and disorders related to excess of divalent metal ions. Among these diseases and disorders are ischemia, stroke, epilepsy and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

; however, there is no conclusive data that the inhibitors of MMPs have been approved for treating the heterogeneity of cancer metastasis in any animal.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that inhibiting the MMPs would result in only the specific types or sites of the interstitial collagen tissue; this kind of treatment can not translated into the treatment of all the heterogeneities of cancer metastasis in regards to their therapeutic effects.

Hence, in the absence of a showing of correlation between all the heterogeneities of cancer metastasis claimed as capable of treatment by the compounds of formula I and the inhibition of matrix metalloproteinase, one of skill in the art is unable to fully predict possible results from the administration of the claimed compounds of formula I due to the unpredictability of the role of inhibiting the MMPs, i.e. whether promotion or inhibition would be beneficial for the treatment of all the heterogeneities of cancer metastasis.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of formula I can inhibit the MMPs which helps in the treatment for all the heterogeneities of cancer metastasis. However, the specification is silent and fails to provide guidance as to whether or not all the heterogeneities of cancer metastasis require only the inhibition of the MMPs for treatment, i.e. the specification fails to provide a correlation between cancer metastasis and the inhibition of the MMPs. Also, there is no direction and guidance for the inhibition of the MMPs for all the heterogeneities of cancer metastasis including any kinds of cancer.

The presence or absence of working examples

There are some conclusive statements for ameliorating disease and conditions related to peripheral inflammatory processes, usefulness in interfering with damaging neuron-inflammatory processes, and the neuron-protective effect for the brain ischemia in vivo test. Furthermore, there are two examples of 3 and 4 which disclose the DP-BAPTA inhibitory activity on MMPs in human glioma cells. But there are no other working examples for the treatment for all the heterogeneities of cancer metastasis in the specification. Also, the compounds disclosed in the specification have no pharmacological data regarding the treatment for all the heterogeneities of cancer metastasis using compounds from various classes and have no data on the possible treatment of various cancers that require the inhibitory activity of various MMPs. Thus, the specification fails to provide sufficient working examples as to how the treatment of all the heterogeneities of cancer metastasis can be treated by the inhibition of various MMPs, i.e. again, there is no correlation between the treatment for all the heterogeneities of cancer metastasis and inhibition of various MMPs.

The breadth of the claims

The breadth of the claims is that the compounds of formula I can treat all the heterogeneities of cancer metastasis by the inhibition of the MMPs , without regards as to the affect of the inhibition of the MMPs on the stated cancer metastasis in treating any types of cancer.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine whether or not the claimed compounds would provide a beneficial treatment of all the heterogeneities of cancer metastasis in treating any types of cancer by the inhibition of the MMPs.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity for treating any types of cancer with respect to all the heterogeneities of cancer metastasis.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of formula I for the treatment of all the heterogeneities of cancer metastasis in any types of cancer by the inhibition of the MMPs. As a result, it necessitates one of the skilled artisans in the art to perform an exhaustive search for selecting the compounds of formula I suitable for treating all the heterogeneities of cancer metastasis in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test whether or not all the heterogeneities of cancer metastasis can be treated by the compounds encompassed in the instant claims, with no assurance of success.

/Taylor Victor Oh/

Primary Examiner, Art Unit 1625

2/15/2010